Supplementary Material 1: Protocol

1. Background

Human Immunodeficiency Virus (HIV) persists as a significant public health threat. There were 511 HIV notifications in Ireland in 2016, giving a rate of 11.2 per 100,000. This is the highest rate ever reported in Ireland.[1] Men who have sex with men (MSM) remain the population most affected by HIV. In 2015, there were 247 new HIV diagnoses reported among MSM, just over half (51%) of all diagnoses in 2015. The number of diagnoses in 2015 was the highest number ever reported among MSM in Ireland and represents an increase of 34% compared to 2014.[1]

Pre-exposure prophylaxis (PrEP) is a biomedical HIV prevention strategy whereby oral anti-retrovirals (namely tenofovir-emtricitabine, Truvada®) are taken daily by HIV-negative individuals to prevent infection. In their latest guidelines, the World Health Organization (WHO) recommends that PrEP containing tenofovir disoproxil fumarate should be offered as part of HIV prevention programmes to people at 'substantial risk of HIV infection'.[2] Of note, PrEP offers no protection against sexually transmitted infections other than HIV.

In August 2016, the European Commission granted marketing authorisation for once-daily Truvada® in combination with safer-sex practices to reduce the risk of sexually acquired HIV-1 infection among uninfected adults at high risk. Therefore Truvada® is licensed for PrEP in Ireland.[3] However, it has not been made available through the Health Service Executive (HSE); no PrEP programme has been implemented and it is not reimbursed through the Primary Care Reimbursement Scheme.

2. Objective

To perform a systematic review of the efficacy of oral antiretroviral pre-exposure prophylaxis (PrEP) therapy to prevent HIV infection in all populations.

3. Methods

A systematic review of Randomised Controlled Trials (RCTs) will be performed. Systematic review will be registered with PROSPERO.

3.1 Criteria for considering studies for this review

Types of studies

RCTs that evaluated the efficacy of antiretroviral chemoprophylaxis in preventing HIV infection in men who have sex with men (MSM).

Types of participants

All populations at increased risk, including MSM transmission (males who have sex with males), transmission between serodiscordant sexual partners, heterosexual transmission, and people who inject drugs.

Types of interventions

Any oral tenofovir-based PrEP regimen.

Types of comparators

Placebo, no PrEP, or alternative medication/dosing schedule.

Types of outcome measures

Primary outcome:

Incidence of new HIV infections.

Secondary outcomes:

1. Adherence to PrEP (as measured by the primary studies)
2. Adverse events associated with PrEP (frequency and type of adverse effects or complications)
3. New STI infections
4. Behaviour change associated with PrEP administration (number of episodes of condomless anal intercourse and number of new sexual partners).

Table 1 outlines the PICOS criteria for inclusion of studies for inclusion.

Table 1: PICOS criteria

PICOS Criteria: Study Selection	
Population	Males who have sex with males, heterosexuals at increased risk, serodiscordant couples, people who inject drugs
Intervention	Pre-exposure prophylaxis (any oral antiretroviral formulation)
Comparator	Placebo, no treatment or alternative medication/dosage schedule
Outcomes	**Primary outcome:** HIV incidence **Secondary outcomes:** 1. Adherence to PrEP (as measured by the primary studies)

	2. Adverse events associated with PrEP (frequency and type of adverse effects or complications) 3. New STI infections 4. Behaviour change reported in RCTs associated with PrEP administration (episodes of condomless anal intercourse and number of new sexual partners)
Studies	Randomised Controlled Trials

3.2 Search methods for identification of studies

Electronic searches

Electronic searches will be conducted in Medline (PubMed), Embase and the Cochrane Register of Controlled Trials. Additional searches will include the CRD DARE Database, Morbidity and Mortality Weekly Report (CDC), Eurosurveillance reports and hand-searching of journals. The WHO International Clinical Trials Registry Platform and ClinicalTrials.gov will be searched for ongoing or prospective trials.

No restrictions will be placed based on location of the intervention. No language restrictions will be used. Articles in languages other than English will be translated where necessary.

The detailed search strategies for each of the databases MEDLINE via PubMed, EMBASE and The Cochrane Central Register of Controlled Trials are as follows:

Table 2: PubMed search strategy

PubMed Search	Queries
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR HIV[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR HIV infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]
#2	Search pre-exposure prophylaxis[tiab] OR preexposure prophylaxis[tiab] OR PREP[tiab] OR anti-retroviral chemoprophylaxis[tiab] OR antiretroviral chemoprophylaxis[tiab] OR chemoprevention[mh] OR chemoprevention[tiab] OR HIV prophylaxis[tiab]
#3	Search tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil
#4	#2 OR #3
#5	#1 AND #4 AND Filters: Clinical Trial, Randomized Controlled Trial, from 1000/1/1 - 2020/7/5

Table 3: Cochrane Central register search strategy

ID	Search
#1	MeSH descriptor HIV Infections explode all trees

#2	MeSH descriptor HIV explode all trees
#3	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME
#4	MeSH descriptor Sexually Transmitted Diseases, Viral, this term only
#5	(#1 OR #2 OR #3 OR #4)
#6	MeSH descriptor Chemoprevention explode all trees
#7	pre-exposure prophylaxis:ti,ab,kw OR preexposure prophylaxis:ti,ab,w OR PREP:ti,ab,kw OR anti-retroviral chemoprophylaxis:ti,ab,kw OR antiretroviral chemoprophylaxis:ti,ab,kw OR hiv prophylaxis:ti,ab,kw
#8	(#6 OR #7)
#9	tenofovir OR TNF OR tenofovir OR PMPA OR viread OR emtricitabine OR EMC OR truvada OR emtriva OR coviracil
#10	(#8 OR #9)
#11	(#5 AND #10)

Table 4: Embase search strategy

No.	Query
#1	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus' OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab
#2	random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over*:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/de OR 'crossover procedure' OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomised controlled trial'/de OR 'randomised controlled trial' OR allocat*:ti OR allocat*:ab
#3	'pre-exposure prophylaxis' OR 'preexposure prophylaxis' OR prep OR 'anti-retroviral chemoprophylaxis' OR 'antiretroviral chemoprophylaxis' OR 'chemoprevention'/syn OR 'hiv prophylaxis' OR 'chemoprophylaxis'/syn
#4	'tenofovir'/syn OR tnf OR Tenofovir OR 'pmpa'/syn OR 'viread'/syn OR 'emtricitabine'/syn OR emc OR 'truvada'/syn OR 'emtriva'/syn OR 'coviracil'/syn
#5	#3 OR #4
#6	#1 AND #2 AND #5

Searching other resources

The reference lists of all included studies will be also be searched.

3.3 Data collection

Two reviewers will independently read the titles, abstracts, and descriptor terms of the search output from the different databases to identify potentially eligible studies. Full text articles will be obtained for all citations identified as potentially eligible. Both reviewers will independently inspect these to establish the relevance of the articles according to the pre-specified criteria. Studies will be reviewed for relevance based on study design, types of participants, interventions, and outcome measures. Reasons for excluding potentially relevant studies will be provided in an excluded studies table.

3.4 Data extraction and management

Data will be independently extracted using an agreed pro forma. Both reviewers will verify the extracted data. Extracted information will include the following:

- Study details: citation, study design and setting, time period and source of funding.
- Participant details: study population demographics, risk characteristics, population size and attrition rate.
- Intervention details: type of drug, comparator, dose, duration and route of administration.
- Outcome details: incidence of HIV infection (including type of laboratory tests used to confirm HIV diagnosis before and after administering PrEP), degree of adherence to PrEP, adverse effects, other STI infections.

RevMan software will be used to record extracted data. The reviewers will independently extract the data and enter them into RevMan; all entries will be rechecked by both reviewers, and all disagreements will be resolved by discussion. If results are pooled, a random effects meta-analysis, using the Mantel-Haenzel rate ratio, will be employed. Table 5 summarises the data collection, management and analysis.

Table 5: Data Collection, Management & Analysis

Data Collection and Management

Selection of studies	• Citations will be screened by one reviewer to eliminate clearly irrelevant studies • Two people will independently review the remaining citations per the inclusion criteria • Any disagreements will be resolved by discussion, or if necessary a third reviewer
Data extraction and management	• Data extraction will be performed independently onto a data extraction pro forma by two people • Any disagreements will be resolved by discussion or a third reviewer • RevMan software will be used to record extracted data
Assessment of risk of bias in included studies	• Risk of bias will be assessed using the Cochrane Risk of Bias Tool for RCTs • This will be performed by two people independently, with any disagreement being resolved by discussion or a third party • Small study bias will be assessed using a funnel plot and Egger's test • An overall assessment of the quality of the evidence will be assessed using the GRADE approach†
Measures of treatment effect and data synthesis	• Effect sizes will be expressed as the reduction in relative risk (RR) of HIV infection in the treatment group compared to control • A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in R) • If significant heterogeneity is observed, a narrative metasynthesis will be performed.
Assessment of heterogeneity	• Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs • Statistical heterogeneity will be examined using the I^2 statistic.

†The Cochrane Handbook. Section 12.2.1: The GRADE approach. Available at: http://handbook.cochrane.org/chapter_12/12_2_1_the_grade_approach.htm. Accessed May 2017.

3.5 Assessment of risk of bias in included studies

Two reviewers will independently examine the components of each included trial for risk of bias using a standard form. The Cochrane Risk of Bias tool will be employed. This will include information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the studies will be assessed and classified as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions. Where differences arise, they will be resolved by discussions with the third reviewer.

Table 6 outlines the potential risks of bias that will be assessed in included studies.

Table 6: Risk of Bias

Risk of Bias

Sequence generation	• Adequate: investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelope shuffling, etc. • Inadequate: investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number. • Unclear: insufficient information to permit judgement of the sequence generation process.
Allocation concealment	• Adequate: participants and the investigators enrolling participants cannot foresee assignment (e.g. central allocation; or sequentially numbered, opaque, sealed envelopes). • Inadequate: participants and investigators enrolling participants can foresee upcoming assignment (e.g. an open random allocation schedule (e.g. a list of random numbers); or envelopes were unsealed or nonopaque or not sequentially numbered). • Unclear: insufficient information to permit judgement of the allocation concealment or the method not described
Blinding	• Adequate: blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias. • Inadequate: no blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding. • Unclear: insufficient information to permit judgement of adequacy or otherwise of the blinding.
Incomplete outcome data	• Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups. • Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data. • Unclear: insufficient reporting of attrition or exclusions.
Selective Reporting	• Adequate: a protocol is available which clearly states the primary outcome as the same as in the final trial report. • Inadequate: the primary outcome differs between the protocol and final trial report. • Unclear: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present.
Other sources of bias	• Adequate: there is no evidence of bias from other sources. • Inadequate: there is potential bias present from other sources (e.g. early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design).

An overall assessment of the quality of the evidence will be assessed using the GRADE approach (the Cochrane Handbook, Section 12.2.1: The GRADE approach).

3.6 Measures of treatment effect

Outcome measures for dichotomous data (e.g., rate of HIV infection comparing intervention and comparator groups) will be calculated as a rate ratio (RR) with 95% confidence intervals (CI). A meta-analysis will be performed to provide a pooled risk if there is sufficient homogeneity across studies (all statistical analysis will be performed in Review Manager and R).

3.7 Dealing with missing data

Study authors will be contacted to provide further information on the results.

3.8 Assessment of heterogeneity

Clinical heterogeneity will be assessed by the reviewers based on the description of the interventions in the RCTs. Statistical heterogeneity will be examined using the I^2 statistic.

3.9 Subgroup analysis

Subgroup analyses by population group and adherence will be performed in the estimation of effectiveness.

3.10 Reporting guidelines

Reporting will adhere to the PRISMA guidelines for systematic reviews.[6]

References

1. HIV in Ireland 2016 Report. HPSC, HSE and UCD. Available at: https://www.hpsc.ie/a-z/hivandaids/hivdataandreports/2016reports/HIVIreland_2016.pdf.

2. WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015. Available at: http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf. Accessed May 2017.

3. Truvada: EPAR. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/truvada

4. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339 doi: 10.1136/bmj.b2700